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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,255	09/17/2003	Milton G. Smith	62157.010111	3702

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,255	SMITH, MILTON G.	
	Examiner	Art Unit	
	Gollamudi S Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 14-39 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 14-39 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims included in the prosecution are 14-39.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 14-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,764,693). Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims and pending claims in instant application are drawn to a method of treating a disease or injury induced by pathological free radicals. The patented claims define the cause of the production of the pathological free radicals as due to that caused by a chemical agent or a caustic gas and instant claims define the free radicals as those caused by caustic gas; the patented claims thus, anticipate the specific cause of the free radical production. The patented claims recite specific ranges of the amounts of the components instant claims do not recite any amounts and it would have been obvious to one of ordinary skill in the art that the

amounts are manipulatable parameters and that instant claims encompass the specific ranges recited in the patented claims. The patented claims also define the disease caused by the pathological free radicals and instant claims are generic with respect to the disease. It would have been obvious to one of ordinary skill in the art that the diseases recited in the patented claims encompass generic 'diseases' in instant claims since the same agent is involved in causing the release of the free radicals.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 14-23 and 27-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Halliwell (Free Radicals in Biology and Medicine (1991) or Packer (Proceedings of the Soc. Exper. Biol. Med., 1992) in combination with Woodle (5,013,556), EP 0 455 386 and JP 62178521 (all are of record in the parent application).

Instant claims are drawn to a method of treating a disease or injury (or deleterious effects) induced by pathological free radical reactions in mammals exposed to a caustic gas by using non-enzymatic antioxidants in liposomes. The claims require a combination of two antioxidants or a combination of beta-carotene, vitamin E, glutathione and niacin.

Halliwell teaches the involvement of free radicals in a variety of human diseases. The diseases include inflammation and autoimmune diseases (pages 422-438), ischemia and reoxygenation injury (pages 438-442), cardiac injury (page 442), cerebral injury (page 444), lung damage and adult respiratory distress syndrome (pages 448-449) and cancer (pages 469-472 and 480). Halliwell also discusses the ability of anti-oxidants to react with the free radicals and protect against these radicals. The anti-oxidants taught by Halliwell include ascorbic acid (vitamin C) (page 123), glutathione (page 126), metal ions (page 131), vitamin E and carotenoids on pages 284-286.

Packer teaches interactions among antioxidants in health and disease. Packer also teaches the ability of vitamin E to quench free radicals and the synergistic action of lipid soluble and water-soluble antioxidants. Packer further teaches the diseases involving the free radicals and the effectiveness of antioxidants (note the abstract, pages 271-275).

These two references show the involvement of free radicals in various diseases and the counter acting effects of various antioxidants against the free radicals. What is lacking in Halliwell, or Packer is the specific teaching of the administration of antioxidants in liposomes. Halliwell, and Packer also lack the specific teachings of the combination of antioxidants in the treatment of free radical induced disease conditions. Halliwell and Packer are also silent with regard to the cause for the production of pathological free radicals in host system.

Woodle while disclosing liposomal formulations containing various drugs including water soluble superoxide dismutase (antioxidant) and lipophilic vitamin E

(antioxidant) teaches that the liposomes are sustained release formulations and for the sustained release via the blood stream, the liposome composition is administered intravenously in an amount which provides a suitable drug dosage over the expected delivery time (note the abstract, lines 33-53 on col. 12 and claims).

Motoyama discloses synergistic inhibition of the oxidation in phosphatidylcholine liposomes by a combination of Vitamin E and cysteine; vitamin E is in the lipid bilayer and cysteine is in the aqueous compartment (note the abstract).

EP 0 455 386 teaches that the antioxidants, vitamin C and vitamin E can be encapsulated together in liposomes. Vitamin C is entrained in the aqueous layer and vitamin E in the lipid structure. EP further teaches the reasons for the inclusion of both vitamins C and E in the liposomes (note the abstract, page 2, lines 20-33).

JP 62178521 similarly teaches the encapsulation of both vitamins C and E together in liposomes. These antioxidants prevent the oxidation of hemoglobin (note the abstract).

In essence, the references of Halliwell, and Packer teach the diseases involving free radicals and the function of antioxidants in countering these free radicals. The reference of Woodle teaches that liposomes are sustained release carriers for drugs such as vitamin E (antioxidant) and the intravenous administration of the liposomes. The references of Motoyama, EP and JP teach the combination use of antioxidants and the reasons for such a combination. It would have been obvious to one of ordinary skill in the art to use liposomes as carriers for the delivery of antioxidants to quench the free radicals involved in various diseases where free radicals are involved since liposomes

are sustained delivery devices as taught by Woodle. The use of a combination of antioxidants such as vitamin C and Vitamin E together because of the references of Motoyama, EP and JP each teach that such a combination is known in the art and because of the advantages taught by Motoyama and JP. One of ordinary skill in the art would be motivated further to include combinations of antioxidants along with trace metals since UNIMED teaches the synergistic effect of combinations of anti-oxidants in sustained release preparations. Although none of the references teach the cause of the production of the free radicals, it is deemed obvious to one of ordinary skill in the art that the anti-oxidants would nullify the effect of the free radicals irrespective of the source of the free radicals.

2. Claims 14-23 and 27-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Halliwell (Free Radicals in Biology and Medicine (1991) or Packer (Proceedings of the Soc. Exper. Biol. Med., 1992) in combination with Woodle (5,013,556), EP 0 455 386, JP 62178521 as set forth above, further in view of UNIMED (also of record in the parent application).

The teachings of Halliwell, Packer, Woodle, EP and JP have been discussed above.

UNIMED's advertisement on ONDROX teaches that antioxidants protect against free-radical damage; UNIMED's advertisement also shows the availability of mixtures of several antioxidants in an encapsulated form for sustained release. UNIMED teaches that the amounts of the antioxidants are theoretically synergistic; UNIMED also teaches trace metals in the combination (note the entire advertisement). UNIMED on cover page

also teaches the reasons for the administration of antioxidants. One of ordinary skill in the art would be further motivated to include a combination of anti-oxidants to quench the free radicals since a synergistic effect is taught by UNIMED.

3. Claims 14-23 and 27-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Halliwell (Free Radicals in Biology and Medicine (1991) or Packer (Proceedings of the Soc. Exper. Biol. Med., 1992) in combination with Woodle (5,013,556), EP 0 455 386, JP 62178521 and UNIMED (all are of record), further in view of either Lichtenberger (5,032,585) or Demopoulos (5,326,757) also of record in the parent application.

The teachings of Halliwell, Packer, Woodle, EP, JP and UNIMED have been discussed above.

Lichtenberger while disclosing methods for surfactant replacement therapy using lipid compositions teaches that the addition of *both* lipid and water soluble vitamins (vitamin A, E and C) and other chemical anti-oxidants with the capability of scavenging free radicals can further enhance and prolong the anti-ulcer efficacy of the lipid mixtures, and this is likely because of their ability to prevent the oxidative destruction of unsaturated phospholipids (note the abstract and col. 8, lines 22-29). Lichtenberger further teaches the encapsulation of the components in liposomes (col. 8, line 39 et seq., col. 22, line 34 et seq.).

Demopoulos while disclosing prevention and treatment of restinosis following angioplasty teaches that the administration of both water soluble and fat soluble antioxidants with significantly reduce the radicals, particularly in tissue directly affected

during angioplasty (note the abstract, col. 4, line 66 through col. 6. Line 40, examples and claims).

One of ordinary skill in the art would have been further motivated to included both lipophilic and hydrophilic antioxidants in the liposomal compositions to quench the free radicals involved in various diseases where free radicals are involved since Lichtenberger teaches the use of both types of antioxidants together and Demopoulos teaches the effectiveness of the combination of the antioxidants when administered together in the treatment of restinosis. The examiner also points out that combining two agents serving the same purpose would have been obvious to one of ordinary skill in the art with the expectation of obtaining at least an additive effect (see In re Kerhoven 205 USPQ 1069).

Claims 24-26 and 37-39 are allowable once the double patenting rejection is overcome.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK